Synopsis – Study 16903A

Study Title Interventional, randomised, double-blind, parallel-group study of the efficacy and safety of initial administration of 17 mg vortioxetine intravenously with 10 mg/day vortioxetine orally in patients with Major Depressive Disorder
Investigators 7 principal investigators at 7 sites in 2 countries *Signatory investigator* – [redacted]
Study Sites 7 sites – 2 in Estonia and 5 in Finland
Publications None (as of the date of this report)
Study Period *First patient first visit* – 11 September 2016 (the date when the first *Informed Consent Form* was signed) *Last patient last visit* – 27 April 2017 (the date of the last protocol-specified contact with any patient)
Objectives • *Primary objective*: – To evaluate the early onset of efficacy of vortioxetine 17 mg IV and vortioxetine 10 mg/day oral dose regimen versus placebo IV and vortioxetine 10 mg/day oral dose regimen on depressive symptoms • *Secondary objectives*: – to evaluate the sustained superiority of vortioxetine 17 mg IV and vortioxetine 10 mg/day oral dose regimen versus placebo IV and vortioxetine 10 mg/day oral dose regimen on depressive symptoms – To evaluate the early onset of efficacy of vortioxetine 17 mg IV and vortioxetine 10 mg/day oral dose regimen versus placebo IV and vortioxetine 10 mg/day oral dose regimen on • global clinical impression • anxiety symptoms – To determine population pharmacokinetic parameters of vortioxetine • *Exploratory objective*: – To evaluate the efficacy of vortioxetine 17 mg IV and vortioxetine 10 mg/day oral dose regimen versus placebo IV and vortioxetine 10 mg/day oral dose regimen on cognitive function • *Safety objective*: – To evaluate the safety and tolerability of vortioxetine 17 mg IV and vortioxetine 10 mg/day oral dose regimen

Study Methodology

- This was an interventional, prospective, multi-national, multi-site, randomised, double-blind, parallel-group, fixed-dose study.
- Patients were recruited from outpatient psychiatric settings, either by referals, sites own databases, or by advertising.
- The study consisted of a:
  - Screening Period – 2 to 14-day period from screening to randomisation
  - Treatment Period – 15-day double-blind treatment period with one initial IV administration of 17 mg vortioxetine or placebo and daily oral treatment with vortioxetine 10 mg.
  - Safety Follow-up Period – 4-week period after end of treatment or after withdrawal from the study.
- At the Baseline Visit, patients were equally randomised (1:1) to either of the following two treatment groups: vortioxetine 17 mg single dose (IV) and vortioxetine 10 mg/day (tablet) (the VOR IV + VOR oral group) or placebo single dose (IV) and vortioxetine 10 mg/day (tablet) (the PBO IV + VOR oral group)
- Following the IV infusion, patients stayed hospitalised for approximately 24 hours for close observation. After the hospitalisation period, patients continued the study on an outpatient basis.
- Efficacy and safety data were collected at Days 0, 1, 3, 7, and 14.
- Blood samples were drawn for drug concentration analysis of vortioxetine on Days 0, 1, and 14.

Number of Patients Planned

54 patients were planned for randomisation: 27 in each group

Diagnosis and Main Selection Criterion

Outpatients with a primary diagnosis of recurrent major depressive disorder (MDD) according to DSM-5™ criteria (classification code 296.3x), who:

- had a Montgomery Åsberg Depression Rating Scale (MADRS) total score ≥30 at the Screening Visit and at the Baseline Visit
- were ≥18 and ≤65 years of age
- had had the current major depressive episode (MDE) for ≥3 months
- was an outpatient at a psychiatric setting willing to be hospitalised for 24 hours following the Baseline Visit

Investigational Medicinal Product, Doses and Modes of Administration, Batch Numbers

Vortioxetine – 17 mg single dose; intravenously (IV), concentrate for solution for infusion, 17 mL (17 mg) administered in 250 mL saline; batch No. 2506879

Vortioxetine – 10 mg/day; tablets, orally; batch No. 2448385

Reference Therapy, Dose and Mode of Administration, Batch Number

Placebo – concentrate for solution for infusion, IV; batch No. 2506877

Duration of Treatment

1 single IV dose and 2 weeks oral treatment

Efficacy Assessments

- Montgomery and Åsberg Depression Rating Scale (MADRS)
- Hospital Anxiety and Depression Scale (HADS)
- Clinical Global Impression – Severity of Illness (CGI-S)
- Clinical Global Impression – Global Improvement (CGI-I)
- Digit Symbol Substitution Test (DSST)
- Trail Making Test A (TMT-A)
- Trail Making Test B (TMT-B)

Pharmacokinetic Assessments

- blood sampling for plasma quantification of vortioxetine

Safety Assessments

- Adverse events (AEs), clinical safety laboratory tests, vital signs, electrocardiograms (ECGs), and physical examinations
- Columbia Suicide Severity Rating Scale (C-SSRS)

Endpoints

- *Primary endpoint*:
  - depressive symptoms:
    - change from baseline to Day 7 in MADRS total score
- *Key secondary endpoints*:
  - depressive symptoms, sustained superiority
    - change from baseline to Day 14 in MADRS total score
    - change from baseline to Day 3 in MADRS total score
    - change from baseline to Day 1 in MADRS total score
- *Secondary endpoints*:
  - depressive symptoms:
    - response (defined as a ≥50% decrease in MADRS total score from baseline) at Day 7
    - remission (defined as a MADRS total score ≤10) at Day 7
    - change from baseline to Day 7 in HADS depression subscale score
  - global clinical impression:
    - CGI-I score at Day 7
    - change from baseline to Day 7 in CGI-S score
  - anxiety symptoms:
    - change from baseline to Day 7 in HADS anxiety subscale score
- *Exploratory endpoints*:
  - depressive symptoms:
    - response (defined as a ≥50% decrease in MADRS total score from baseline) at Day 1, 3, and 14
    - remission (defined as a MADRS total score ≤10) at Day 1, 3, and 14, separately
    - change from baseline to Day 1, 3, and 14 in HADS depression subscale score
  - global clinical impression:
    - change from baseline to Day 1, 3, and 14 in CGI-S score
    - CGI-I score at Day 1, 3, and 14
  - anxiety symptoms
    - change from baseline to Day 1, 3, and 14 in HADS anxiety subscale score
  - cognitive function
    - change from baseline to Day 1 and 14 in DSST, number of correct symbols
    - change from baseline to Day 1 and 14 in TMT-A, time
    - change from baseline to Day 1 and 14 in TMT-B, time
- *Safety endpoints*:
  - adverse events
  - absolute values and changes from baseline in clinical safety laboratory tests, vital signs, and ECG parameters
  - potentially clinically significant (PCS) clinical safety laboratory test values, vital signs, and ECG parameter values
  - C-SSRS categorisation based on Columbia Classification Algorithm of Suicide Assessment (C-CASA) definitions

Statistical Methodology

- The following analysis sets were used:
  - *all-patients-randomised set* (APRS) – all randomised patients
  - *all-patients-treated set* (APTS) – all patients in the APRS who took at least one tablet or received infusion
  - *full-analysis set* (FAS) – all patients in the APTS who had a valid baseline assessment and at least one valid post-baseline assessment of the MADRS total score before or at Day 7 and who had taken at least one tablet and received infusion
- All efficacy analyses were based on the FAS and the safety analyses were based on the APTS.
- *Analyses of the primary and key secondary endpoints:*
  - The change from baseline in MADRS total score were analysed using a restricted maximum likelihood (REML)-based mixed model for repeated measures (MMRM) approach. The model included the following fixed effects: site, day (1, 3, 7, and 14), and treatment as factors, baseline MADRS total score as a continuous covariate, treatment-by-day interaction, and baseline MADRS total score-by-day interaction. An unstructured covariance structure was used to model the within-patient errors. The Kenward-Roger approximation was used to estimate denominator degrees of freedom. The analysis was based on the missing-at-random (MAR) assumption including all available observations (observed cases [OC]).
- *Testing strategy:*
  - The following sequence of hierarchically ordered primary and key secondary endpoints was used:
    - change from baseline to Day 7 in MADRS total score (primary)
    - change from baseline to Day 14 in MADRS total score
    - change from baseline to Day 3 in MADRS total score
    - change from baseline to Day 1 in MADRS total score
  - The overall 5% level of significance was kept by only continuing as long as significance was obtained at 5% at each step.
- *Analyses of secondary and exploratory endpoints:*
  - For continuous endpoints (all endpoints except response and remission), the same methodology as that described for the primary and key secondary endpoints were used. For analyses of CGI-I, the baseline measure for CGI-S was included as baseline assessment covariate.
  - For binary endpoints (response and remission), logistic regression with treatment as a factor and the baseline score as a covariate was used. The logistic regression was made for OC, last observation carried forward (LOCF), and NRI. For both response and remission an empty assessment was imputed for the NRI as a 'No'.
  - The DSST change from baseline was also analysed using an analysis of covariance (ANCOVA [OC]) at Day 1 and Day 14 separately with treatment and site as factors and baseline DSST score, baseline MADRS total score, and change from baseline in MADRS total score at Day 1 and Day 14, respectively, as covariates.

Patient Disposition and Analysis Sets

- Patient disposition is summarised below:

	PBO IV + VOR oral		VOR IV + VOR oral		Total	
	n	(%)	n	(%)	n	(%)
Patients randomised	28		27		55	
Patients treated (all-patients-treated set [APTS])						
Patients completed	28	(100)	26	(96.3)	54	(98.2)
Patients withdrawn	-	-	1	(3.7)	1	(1.8)
Primary reason for withdrawal:						
Lost to follow-up	-	-	1	(3.7)	1	(1.8)
Analysis sets:						
APTS	28		27		55	
Full-analysis set (FAS)	28		27		55	

Demography and Baseline Characteristics of the Study Population

- The mean age of the patients were approximately 45 years. The majority of the patients were women and all patients were White.
- There were no notable differences between the treatment groups in the baseline assessments of height, weight, and body mass index (BMI).
- The median duration of the current MDE was approximately 22 weeks in both treatment groups. The mean number of previous episodes was 2.8
- The baseline efficacy scores were comparable between the treatment groups. The mean MADRS score of 34 points indicated that the patients had *moderate* to *severe* MDD and the mean CGI-S score of 5 points indicated that the patients were *markedly* to *severely* ill.

Efficacy Results

- The results of the primary and key secondary endpoints are summarised below:

	Change from Baseline			Difference to PBO IV + VOR Oral		
	Day	**N**	**Mean (SE)**	**Difference (SE)**	**95% CI**	**p-value**
PBO IV + VOR oral	1	28	-5.9 (1.2)			
	3	28	-10.7 (1.6)			
	7	28	-13.8 (1.8)			
	14	28	-18.2 (1.7)			
VOR IV + VOR oral	1	27	-7.2 (1.3)	-1.3 (1.3)	(-3.9; 1.4)	0.3391
	3	26	-12.3 (1.7)	-1.6 (2.0)	(-5.7; 2.4)	0.4242
	7	26	-14.0 (1.9)	-0.2 (2.3)	(-5.0; 4.5)	0.9197
	14	26	-17.1 (1.8)	1.1 (2.2)	(-3.3; 5.6)	0.6131

- The study (n=55) did not show a statistically significant difference between the VOR IV + VOR oral group and the PBO IV + VOR oral group in the analyses of the primary and key secondary endpoints, change from baseline in MADRS total score at Day 7, 14, 3, and 1, respectively. However, numerical advantages were seen at Day 1 and 3 for the VOR IV + VOR oral group.
- There was a fast and marked decline (improvement) in MADRS total score in both treatment groups. However, numerical advantages were seen at Day 1 and 3 for the VOR IV + VOR oral group.
- In the analysis of the secondary and exploratory endpoints related to global clinical impression, response and remission, patient-reported depressive and anxiety symptoms, and cognitive function, there were no statistically significant differences between the treatment groups. However, numerical differences in favor of the VOR IV + VOR oral group were seen at the early timepoints for several endpoints.
- Plasma exposure, in terms of Cmax, was on average 4.3, 1.4, 1.1, and 1.0 times higher for the VOR IV + VOR oral group compared to the PBO IV + VOR oral group at Day 0, Day 3, Day 7, and Day 14, respectively.

Pharmacokinetic/Pharmacodynamic Results

- The plasma exposure results of vortioxetine are summarised below:

Parameter	PBO IV + VOR Oral	VOR IV + VOR Oral
$AUC_{0\text{-}24}$ (ng*h/mL)	47 ± 20	251 ± 49
$AUC_{0\text{-}72}$ (ng*h/mL)	289 ± 93	715 ± 166
$AUC_{0\text{-}168}$ (ng*h/mL)	1050 ± 336	1666 ± 475
$AUC_{0\text{-}336}$ (ng*h/mL)	2715 ± 927	3368 ± 1149
$AUC_{0\text{-}\tau,\ Day\ 3}$ (ng*h/mL)	153 ± 48	211 ± 65
$AUC_{0\text{-}\tau,\ Day\ 7}$ (ng*h/mL)	205 ± 71	222 ± 82
$AUC_{0\text{-}\tau,\ Day\ 14}$ (ng*h/mL)	230 ± 85	244 ± 106
$C_{max,\ Day\ 0}$	2.8 ± 1.1	12 ± 2.3
$C_{max,\ Day\ 3}$	7.2 ± 2.4	10 ± 3.0
$C_{max,\ Day\ 7}$	9.6 ± 3.4	11 ± 3.8
$C_{max,\ Day\ 14}$	11 ± 4.0	11 ± 4.7

- Plasma exposure, in terms of C_{max}, was on average 4.3, 1.4, 1.1, and 1.0 times higher for the VOR IV + VOR oral group compared to the PBO IV + VOR oral group at Day 0, Day 3, Day 7, and Day 14, respectively.

Safety Results

- The adverse event incidence in the Treatment Period is summarised below:

	PBO IV + VOR oral		VOR IV + VOR oral	
	n	(%)	n	(%)
Patients treated	28		27	
Patients who died	0		0	
Patients with treatment-emergent serious AEs (SAEs)	0		0	
Patients with treatment-emergent adverse events (TEAEs)	18	(64.3)	21	(77.8)
Total number of TEAEs	42		38	

- No SAEs occurred during the study and none of the patients withdrew due to adverse events.
- The incidence of TEAEs in the treatment period was 64% (18 patients) in the PBO IV + VOR oral group and 78% (21 patients) in the VOR IV + VOR oral group.
- The most common TEAE in both treatment groups was nausea reported by 32% (9 patients) of the patients in the PBO IV + VOR oral group and 48% (13 patients) of the patients in the VOR IV + VOR oral group.
- A high proportion of the patients with nausea in the VOR IV + VOR oral group had nausea for a short duration (≤1 day). The onset of nausea occurred on Day 1 in 9 out of 13 patients in the VOR IV + VOR oral group and in 5 out of 9 patients in PBO IV + VOR oral group. All events of nausea were *mild* to *moderate* and the severity was not different between the groups. As for the other adverse events of special interest, there was one patient in the PBO IV + VOR oral group who had erectile dysfunction; no patients had insomnia.
- The majority of the TEAEs were mild or moderate; 2 patients in the VOR IV + VOR oral group had severe TEAEs (anxiety and fatigue, respectively).
- There were no notable findings in the clinical safety laboratory tests, vital signs, or ECG parameters.
- The TEAEs with an incidence ≥5% in any treatment group are summarised below:

Preferred Term	PBO IV + VOR oral		VOR IV + VOR oral	
(MedDRA Version 19.0)	n	(%)	n	(%)
Patients treated	28		27	
Nausea	9	(32.1)	13	(48.1)
Headache	4	(14.3)	4	(14.8)
Anxiety	1	(3.6)	3	(11.1)
Diarrhoea	1	(3.6)	3	(11.1)
Fatigue	4	(14.3)	2	(7.4)
Somnolence	1	(3.6)	2	(7.4)
Tachycardia	1	(3.6)	2	(7.4)
Nasopharyngitis	4	(14.3)	1	(3.7)
Erectile Dysfunction (sex specific)	1	(20.0)	0	-
Hyperhidrosis	2	(7.1)	0	-

Conclusions

- In this study (n = 55), the VOR IV + VOR oral group was not superior to the PBO IV + VOR oral group in the analysis of early onset of efficacy on depressive symptoms. Thus there was no statistically significant difference between the treatment groups in the analyses of the primary and key secondary endpoints, change from baseline in MADRS total score at Day 7, 14, 3, and 1, respectively. However, numerical advantages were seen at Day 1 and 3 for the VOR IV + VOR oral group.
- The results of the secondary and exploratory endpoints evaluating global clinical impression, patient-reported depressive and anxiety symptoms, and cognitive function where in line with those of the primary and key secondary endpoints.
- The vortioxetine 17 mg IV followed by vortioxetine 10 mg/day dosing regimen was safe and well-tolerated in this 2 weeks study in patients with MDD.

Report Date
16 October 2017
This study was conducted in compliance with the principles of *Good Clinical Practice*.